IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Appellants	:	BARTHOLOMAUS et al.
Serial No.	:	10/596,202 (U.S. Patent App. Publ. 2008-0286342)
Filing Date	:	2 June 2006
For	:	**FORM OF ADMINISTRATION BASED ON CROSSLINKED HYDROPHILIC POLYMERS**
Examiner	:	SULLIVAN, Danielle
Art Unit	:	1616

745 Fifth Avenue
New York, New York 10151

Filed via EFS-Web
15 June 2011

APPEAL BRIEF UNDER 37 C.F.R. 41.37

Mail Stop: Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is being filed in response to the final rejection of claims 1-14 in the Office Action dated 15 November 2010 and Notice of Appeal filed on 15 April 2011.

The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0320.

(I) REAL PARTY IN INTEREST

The real party in interest in this appeal is the assignee, LTS Lohmann Therapie-Systeme AG, who is the owner of this application by assignment from the inventor (Reel 017714/Frame 0768).

(II) RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any related appeals or interferences which directly affect or are directly affected by or have bearing on the Board's decision in the pending appeal.

(III) STATUS OF CLAIMS

Claims 1-14 were finally rejected in the Office Action mailed 15 November 2010. The appellants filed an after final response on 14 January 2011, but did not amendment the claims.

(IV) STATUS OF AMENDMENTS

The amendment/response of 14 January 2011 was entered and it is believed that all other amendments have been entered.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is the only independent claim under Appeal and is directed to a process for producing a dosage form in film form for surface administration of at least one active ingredient and/or nutrient to a living creature comprising at least one active ingredient-containing and/or nutrient-containing layer based on hydrophilic polymers crosslinked with at least one polyacrylic acid derivative by building up individual layers successively on a smooth surface, characterized by the steps:

a) simultaneous spraying of
   (1) an aqueous solution of the hydrophilic polymers and of the active ingredient and/or of the nutrient and
   (2) of an aqueous solution of the polyacrylic acid derivative, wherein the aqueous solution of the hydrophilic polymers and of the active ingredient and/or of the nutrient and aqueous solution of the polyacrylic acid derivative are mixed after spraying and the hydrophilic polymers are crosslinked by the polyacrylic acid derivative *in situ*; and

b) removal of the water by drying.

Support for this claim can be found throughout the specification, e.g., page 1, lines 30-38, page 15, lines 1-17 and original claim 1.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The only remaining issue remaining to be decided is whether claims 1-14 were properly rejection as being obvious over Nara et al. (US 6,245,351 -"Nara") in view of Rupprecht et al. (DE 101 46 251 - "Rupprecht").

NOTE: References to location of text from Rupprecht in this Appeal Brief refer to the machine translation of DE 101 46 251 which was provided by the Examiner as part of the Office Action mailed 15 November 2010.

(VII) ARGUMENTS

Claims 1-14 were rejected as allegedly being obvious by Nara et al. (US 6,245,351 - "Nara") in view of Rupprecht et al. (DE 101 46 251 - "Rupprecht"). The appellants request reconsideration of this rejection for the following reasons.

Reference to the "final rejection" refers to the Office Action mailed on 15 November 2010.

I. Legal Standards for Determining Obviousness

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385 (2007), the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(A) Determining the scope and contents of the prior art;
(B) Ascertaining the differences between the prior art and the claims in issue;
(C) Resolving the level of ordinary skill in the art; and
(D) Evaluating evidence of secondary considerations.

"When evaluating the scope of a claim, every limitation in the claim must be considered. USPTO personnel may not dissect a claimed invention into discrete elements and then evaluate the elements in isolation. Instead, the claim as a whole must be considered. See, e.g., *Diamond v. Diehr*, 450 U.S. 175, 188-89, 209 USPQ 1, 9 (1981)." *See* MPEP 2106.

When ascertaining the differences between the prior art and the claims in issue, both the claimed invention and the prior art are considered as a whole. *See* 35 U.S.C 103(a).

Once the *Graham* factual inquiries are resolved, Office personnel then must determine whether the claimed invention would have been obvious to one of ordinary skill in the art.

II. Consideration of the claim 1 and the prior art as a whole

Claim 1 is an independent claim directed toward a process of producing a dosage form which can broken down into the following elements (claim 1 as presented in the "Claims Appendix" is reproduced below in reformatted form):

A process

for producing a dosage form

in film form

for surface administration of at least one active ingredient and/or nutrient to a living creature

comprising at least one active ingredient-containing and/or nutrient-containing layer based on hydrophilic polymers crosslinked with at least one polyacrylic acid derivative by building up individual layers successively on a smooth surface,

characterized by the steps:

a) simultaneous spraying of

(1) an aqueous solution of the hydrophilic polymers and of the active ingredient and/or of the nutrient and

(2) of an aqueous solution of the polyacrylic acid derivative, wherein the aqueous solution of the hydrophilic polymers and of the active ingredient and/or of the

nutrient and aqueous solution of the polyacrylic acid derivative are mixed after spraying and

the hydrophilic polymers are crosslinked by the polyacrylic acid derivative *in situ*; and

b) removal of the water by drying.

(This application has been given a primary classification of 424/464 (Tablets, Lozenges, or Pills) which is a subclass of 424/400 (Preparations Characterized by **Special Physical Form**). According to the "Search Notes" in PAIR, 424/464 is the only class/subclass searched)

When considering the Nara and Rupprecht as a whole, it is clear that Nara is directed toward an ***enteric capsule*** consisting of a drug core with an outer coating which is identified in the "Summary of the Invention" (see col. 1, lines 50-57 of Nara – "…to develop a controlled-release composition for ***oral administration*** coated with a coating composition which is capable of releasing drug at higher rates in the ***intestinal tract*** than in the stomach to maintain an almost constant plasma concentration of drug and ensure effect of drug in the body for an extended period of time.")

Nara's primary classification is 424/461 (Containing polysaccharides (e.g. cellulose sugars, etc.)) which is a subclass of 424/451 (Capsules (e.g. of gelatin, of chocolate, etc.) which in turn is a subclass of 424/400 (Preparations Characterized by **Special Physical Form**).

Rupprecht is relied upon by the Examiner for teaching "…a device for making drug films with at least one spraying device for forming a film forming polymer and drying it **(page 1, paragraph 1)**. The solutions are sprayed simultaneously using two-nozzles systems preferably because they provide uniform distributions of the film-formed components and other components may be crosslinked **(page 1, paragraph 14)**." (page 5, lines 10-14 of the final rejection).

However, these respective passages from Rupprecht actually recite:

Page 1, paragraph 1

"The instant invention concerns a device to the production of a wirkstoffhaltigen, preferably pharmaceutical film exhibiting at least a spraying device for spraying at least a film forming

polymer, if necessary, other film-formed components and at least active ingredient or their corresponding solutions, driers and conveyor belt, with which at least a plate, becomes applied on which the film, becomes transported." ("wirkstoffhaltigen" refers to containing an active substance)

Page 1, paragraph 14

"Further prefered (sic) exhibits the device according to invention means, with which the jet point of impact on the plate is more adjustable. By this adjustment one becomes if possible uniform distribution of the film-formed components on the plate achieved. If the film not only from film forming polymers, but if necessary, for other components, like z.B. with the polymers responsive crosslinkers, constructed, should the jet point of impact of the corresponding solutions is be as congruent as possible and the adjustment of the nozzles a simultaneous spraying of the solutions preferably permit." ("z.B" = zum Beispiel, i.e. for instance/for example)

As such, Rupprecht is merely referring to a generic method of forming a drug film by spraying an active agent containing solution onto a substrate (plate) which is moving by means of a conveyer belt and drying solution sprayed onto the substrate; if other components, e.g., crosslinkers are used, the nozzle is set as congruent as possible.

III. Differences between the prior art and the appellants' claims

After making the as a whole consideration of Nara, Rupprecht and the appellants' claim 1, it is clear that Nara differs from the appellants' claims in that Nara does not teach:

(1) simultaneous spraying of 1) and 2) and mixing the solutions after spraying; and

(2) the dosage being in film form.

These differences are acknowledged by the Examiner (see page 5, lines 6-8 of the final rejection). Rupprecht is cited in the final rejection to address these differences (see page 5, lines 8-9)

However, there are additional differences which were not acknowledged in the Office Actions.

First, the presently claimed invention is a film form for **surface administration** whereas Nara is directed toward an enteric composition, i.e. intended for oral administration and having the ability to pass through the acidic environment of the stomach for delivery into the small intestine.

Second, there is no teaching from Nara to mix an aqueous solution of hydrophilic polymers and active ingredient/nutrient with an aqueous solution of polyacrylic acid derivative.

Third, there is no teaching from Nara that the hydrophilic polymers and polyacrylic acid derivative are crosslinked.

Fourth, there is no teaching from Nara that the crosslinking occurs *in situ*.

Fifth, there is no teaching from Nara for the elements represented by dependent claims 10-13, e.g. based on the dependencies of the claims, claim 13 includes not only all of the elements of claim 1, but also claims 2, 10, 11, 12 and 13.

IV. Fact pattern of the present application are not analogous to the fact pattern of *In re Stover*

The entirety of the Examiner's substantive portion of her "Response to Arguments" section stated "Applicant argues Nara is related to a dosage form of an enteric capsule and Horstmann was directed to a sheet-like administration forms which are completely different. The Examiner is not persuaded by this argument because both Nara and Horstmann are related teach drug formulations that differ in shape, not composition. In view of *In re Stover*, 56 USPQ 525 (C.C.P.A), it is a matter of choice and not inventions to select any particular shape desired in the finished product." (see page 2, lines 16-22 of the final rejection)

While the Examiner is certainly not limited to reciting case law cited in Appendix II (List of Decisions Cited) of the MPEP, the appellants note that *In re Stover*, 146 F.2d 299, 56 USPQ 525 (CCPA 1944) is not among the decisions cited.

Furthermore, MPEP 2144.04 states in part that "...if the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." However, the facts in *Stover* are not sufficiently similar to those in the application under examination.

The appellants note that case law with regard to design changes, shapes and sizes are often in the context of the mechanical arts and *Stover* is no different.

The claims in *Stover* related to an elongated paper container particularly adapted for receiving and packaging ice cream, or other plastic foodstuffs, for subsequent sale to the public in sanitary and predetermined units. *Id.* @ 300.

The CCPA upheld the Board in *Stover* which "...decided that it would not amount to invention to provide the container of Clearwater with the markings as taught by Tiffany, and

with the vents or openings for the escape of air as taught by Ortner or Massey, and that no patentable conception is involved in filling a container through the urge of gravity, as that procedure is but a common expedient for filling containers with a liquid or semiliquid substance. The rejected claims herein cover an article, the construction of which, in view of the prior art, would be within the obvious and expected routine skill of those laboring in the art, and are, therefore, unpatentable." *Id. @* 301-302.

As such, the facts of *Stover* do not resemble the facts of the presently claimed application.

Unlike the design choice for a mechanical device in *Stover*, the Examiner here is attempting to provide an equivalency for all forms of pharmaceutical dosage forms which would be unrecognizable to those of ordinary skill in the pharmaceutical arts.

Whole industries have been built on selecting and developing a specific form of drug delivery methods and as such one of ordinary skill in the art concerned with the formation of enteric capsules as in Nara would not use the teachings of Rupprecht (or any other film forming prior art) as this does not assist in the production of a completely different pharmaceutical dosage delivery form (i.e. capsule vs. film). By way of example, the appellants' provided a copy of the table of contents from *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (Eighth Edition)*, ed. Allen et al. (2005)) as part of their response filed on 14 January 2011 (provided here as Exhibit A)

The differences in pharmaceutical dosage delivery forms is also recognized by the PTO's classification system, Class 424, subclass 400 (Preparations Characterized by **Special Physical Form**). These differences appear to be acknowledged by the Examiner as she never searched the class/subclasses cited in the U.S. classification or Field of Search for the Nara patent nor did the Examiner of the Nara patent ever search in the class/subclass of the present application.

The appellants do not suggest that prior art from differing classes/subclasses can never be used in combination, but for the presently claimed invention, the modifications required to be made for the combination of Nara and Rupprecht would not be obvious to one of ordinary skill in the art as their respective pharmaceutical dosage forms are so vastly different; one of ordinary skill in the art would not be able to magically select a single element or teaching from Rupprecht directed toward the making of **films** and have a reasonable expectation of success that

combination would be applicable for an **enteric composition** such as that described by Nara while maintaining the enteric properties of Nara.

Moreover, the PTO has provided guidance with respect to determinations of obviousness that after evidence or argument is submitted by the appellant in response, patentability is determined on the totality of the record, by a preponderance of evidence (more likely than not) with due consideration to persuasiveness of argument. See *In re Spada*, supra; *In re Corkill*, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed.Cir.1985); *In re Caveney*, 761 F.2d 671, 674, 226 USPQ 1, 3 (Fed.Cir.1985); *In re Johnson*, 747 F.2d 1456, 1460, 223 USPQ 1260, 1263 (Fed.Cir.1984). *See* MPEP 2106.

There is no indication that the totality of the evidence was considered and that the reestablishment of the *prima facie* holding of obviousness was based solely on analogy to a legal decision whose factual circumstance is not related to the present factual circumstance. For this reason alone, the rejection based on the combination of Nara and Rupprecht should be withdrawn.

V. The combination of Nara and Rupprecht never established a *prima facie* holding of obviousness

Once differences are identified between the claimed invention and the prior art, those differences must be assessed and resolved in light of the knowledge possessed by a person of ordinary skill in the art. Against this backdrop, one must determine whether the invention would have been obvious at the time the invention was made. If not, the claimed invention satisfies 35 U.S.C. 103. "As discussed in *In re Piasecki* (745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984)) the examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a prima facie case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant. *See* MPEP 2106.

However, at best, the Examiner merely raised some indication of non-obviousness; the Examiner never provided the evidence necessary to meet the preponderance of evidence standard necessary to establish a *prima facie* holding of obviousness (much less reestablish this holding after the appellants' reply during prosecution).

First, the difference between Nara and the claimed invention is not limited merely to the step of drying the mixture or that the dosage is in film form for surface/topical administration

(which are substantial differences in and of themselves), but also includes the additional differences that:

(1) the hydrophilic polymers crosslinked with at least one polyacrylic acid derivative (and for the claims as amended, the hydrophilic polymers are crosslinked by the polyacrylic acid derivative *in situ*)[1]; and

(2) there is no mention of the simultaneous spraying of an aqueous solution of the hydrophilic polymers and aqueous solution of the polyacrylic acid derivative.

Nara also differs from the appellants' claimed invention in that their method for producing their unrelated composition does so in a manner which teaches away from either Rupprecht or the appellants' claimed process. Nara prepares a drug-containing core following by spray-coating the resulting core with a liquid coating composition; for illustrative purposes see Example 3 (col. 9, lines 8-13) and Example 7 (col. 10. lines 43-48) – "These core granules were placed in a spiral flow type coating machine and spray coated with hydroxypropylmethylcellulose dissolved in a mixture of ethanol and water…to yield coated granules.".

What Nara is teaching is an active agent in an inner core which is an element not taught in Rupprecht or in the appellants' claimed invention and Nara does not suggest the active agent being in anything which would be considered equivalent to a film.

As Rupprecht does not address these differences, the combination of Nara and Rupprecht do not render the appellants' claims for this reason alone as all claim elements are not taught or suggested by the combination of Nara and Rupprecht. Moreover, in the context of Nara's invention, it would be nonsensical to place the active ingredient in a film which coats Nara's inner core as this film is destroyed in providing the enteric effect in allowing the composition to pass through the stomach acidic environment and would only serve to waste valuable active ingredient.

In addition, even if Rupprecht had taught all the missing elements, when considering Nara as a whole, it is not even related to the type of dosage forms which is taught both by the appellants' claimed invention and by Rupprecht (i.e. film forms). Nara refers to an alternative

[1] Moreover, there appeared to be a misunderstanding in the Office Action about the teaching within Nara about crosslinking. The liquid coating composition used by Nara comprises of a water-insoluble substance, swellable polymer and an ***already crosslinked polymer***, i.e. the swellable polymer is ***not crosslinked*** to the crosslinked polymer.

form of an ***enteric*** capsule consisting of a drug core with an outer coating which is clearly identified in the "Summary of the Invention" (see col. 1, lines 50-57 – "…to develop a controlled-release composition for ***oral administration*** coated with a coating composition which is capable of releasing drug at higher rates in the ***intestinal tract*** than in the stomach to maintain an almost constant plasma concentration of drug and ensure effect of drug in the body for an extended period of time.")

In contrast, Rupprecht is directed to a device for making films and only generically refers to the film making process which is completely different than the controlled-release compositions of Nara. Even if one of ordinary skill in the art were permitted to pick and choose elements from the combination of Nara and Rupprecht at will, the skilled artisan still would not achieve the appellants' claimed process steps of claims 1-4 and 10-13, nor would they obtain the products formed by the process.

Moreover, one of ordinary skill in the art would not look to use Rupprechts' device to make modifications to the invention of Nara, given the differences in forms, as there is no expectation of success that taking an isolated element from Rupprecht could be incorporated into the controlled-release composition of Nara while maintaining the intended use of Nara, i.e. releasing drug at higher rates in the ***intestinal tract*** than in the stomach to maintain an almost constant plasma concentration of drug.

Therefore, it would not have been obvious to combine Rupprecht with Nara as there was no reason to combine teachings from disparate inventions nor was there a reasonable expectation of success for the combination proffered in the Office Action.

(VIII) CLAIMS APPENDIX

1. (Previously presented) A process for producing a dosage form in film form for surface administration of at least one active ingredient and/or nutrient to a living creature comprising at least one active ingredient-containing and/or nutrient-containing layer based on hydrophilic polymers crosslinked with at least one polyacrylic acid derivative by building up individual layers successively on a smooth surface, characterized by the steps:

a) simultaneous spraying of (1) an aqueous solution of the hydrophilic polymers and of the active ingredient and/or of the nutrient and (2) of an aqueous solution of the polyacrylic acid derivative, wherein the aqueous solution of the hydrophilic polymers and of the active ingredient and/or of the nutrient and aqueous solution of the polyacrylic acid derivative are mixed after spraying and the hydrophilic polymers are crosslinked by the polyacrylic acid derivative *in situ*; and
b) removal of the water by drying.

2. (Previously presented) The production process as claimed in claim 1, characterized in that an optionally crosslinked polyacrylic acid is used as polyacrylic acid derivative.

3. (Previously presented) The production process as claimed in claim 1, characterized in that hydroxypropylmethylcellulose, hydroxyethylcellulose and/or methylcellulose is employed as hydrophilic polymer.

4. (Previously presented) The production process as claimed in claim 1, characterized in that the weight ratio of hydrophilic polymers to polyacrylic acid derivative(s) is from 5:1 to 5:4.

5. (Previously presented) A dosage form produced as claimed in claim 1.

6. (Previously presented) The dosage form as claimed in claim 5, characterized in that it has at least one active ingredient-containing and/or nutrient-containing layer, a covering layer and optionally an adhesive layer.

7. (Previously presented) The dosage form as claimed in claim 5, characterized in that at least one active ingredient-containing layer has a concentration gradient of the active ingredient.

8. (Previously presented) The dosage form as claimed in claim 5, characterized in that the covering layer is impermeable for the active ingredient and/or nutrient.

9. (Previously presented) The dosage form as claimed in claim 5, characterized in that the dosage form is covered with a protective layer before application.

10. (Previously presented) The production process as claimed in claim 2, characterized in that the optionally crosslinked polyacrylic acid, is a polyacrylic acid crosslinked with allylsucrose or allylpentaerythritol and/or a polyacrylic acid crosslinked with divinylglycol, optionally neutralized with calcium.

11. (Previously presented) The production process as claimed in claim 10, characterized in that hydroxypropylmethylcellulose is employed as hydrophilic polymer.

12. (Previously presented) The production process as claimed in claim 11, characterized in that the weight ratio of hydrophilic polymers to polyacrylic acid derivative(s) is from 5:2 to 5:3.

13. (Previously presented) The production process as claimed in claim 12, characterized in that the dosage form has a tear strength greater than 40 N.

14. (Previously presented) The dosage form as claimed in claim 5, characterized in that the dosage form has a tear strength greater than 40 N.

(IX) EVIDENCE APPENDIX

Exhibit A - *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (Eighth Edition)*, Table of Contents, ed. Allen et al. (2005))

(X) RELATED PROCEEDINGS APPENDIX

None

CONCLUSION

In view of the foregoing, it is respectfully submitted that the claims on appeal are patentable and that the rejection under 35 U.S.C. §103(a) should be reversed.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

Attorney for Appellant

By: /Howard C. Lee/

Marilyn Matthes Brogan
Reg. No. 31,223
(212) 588-0800
Fax (212) 588-0500

Howard C. Lee
Reg. No. 48,104